

The opinion in support of the decision being entered today
is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KANWAL K. RAINA and AMMAR DERRAA

Appeal 2007-0913
Application 09/888,126
Technology Center 1600

Decided: July 24, 2007

Before DONALD E. ADAMS, LORA M. GREEN, and NANCY J. LINCK,
Administrative Patent Judges.

GREEN, *Administrative Patent Judge.*

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the
Examiner's final rejection of claims 1, 3-18, 20-39, and 41-60.¹ We have

¹ This case is related to USSN 10/179,463, Appeal No. 2007-0854. Both Appeals were heard together, and have been considered and decided concurrently.

jurisdiction under 35 U.S.C. § 6(b). Claims 1 and 18 are representative of the claims on appeal, and read as follows:

1. A formulation having particles comprising, by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate.

18. A method for treating a human patient in need of insulin comprising administering pulmonarily to the respiratory tract of a patient in need of treatment, in a single, breath actuated step an effective amount of particles comprising by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate, wherein release of the insulin is rapid.

The Examiner relies upon the following art in rejecting the claims:

Edwards	US 5,985,309	Nov. 16, 1999
Patton	US 5,997,848	Dec. 7, 1999

We affirm.

ISSUE

The Examiner contends that the invention as claimed is obvious over the combination of Edwards and Patton, and that Appellants have not rebutted the prima facie case.

Appellants contend that the Declaration of Jennifer L. Schmitke, submitted under 37 C.F.R. § 1.132 and dated April 20, 2004, rebuts the Examiner's prima facie case of obviousness by demonstrating that the claimed composition has unexpected properties.

The issue is thus whether Appellants have demonstrated unexpected results as to the insulin formulation being claimed, thus rebutting the Examiner's case of prima facie obviousness.

FACTS

The Examiner rejected claims 1, 3-18, 20-39, and 41-60 under 35 U.S.C. § 103(a) as being obvious over Patton in view of Edwards (Office Action mailed August 11, 2004, 2).²

The Examiner relies on Patton for teaching the systemic delivery of insulin to a mammalian host through the inhalation of a dry powder that is rapidly absorbed through the alveolar regions of the lung (Office Action dated August 11, 2004, 2). The dry powder containing insulin is prepared by dissolving insulin in an aqueous buffer to form a solution and then spray drying the solution to produce substantially amorphous particles (*id.*). According to the Examiner, the pharmaceutical carrier, which may be an amino acid such as glycine, lysine, etc., may be optionally dissolved in the buffer, typically a citrate buffer such as sodium citrate, to form a homogenous solution, “wherein spray drying of the solution produces individual particles comprising insulin, carrier buffer and any other compounds which were preset in the solution.” (*Id.* at 2-3.)

Patton is also cited for teaching that dry powders of insulin that may be used include amorphous insulin, crystalline insulin, and mixtures thereof (*id.* at 2). The insulin concentration may range from 5 to 95%, preferably from 20 to 80%, with the carrier material ranging from 5 to 95% (*id.* at 3). The Examiner notes that “Patton, while teaching amino acids as carriers, lacks disclosure on DPPC.” (*Id.*)

² Claims 1, 3-18, 20-39, and 41-60 also stood rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending 10/179,463 in view of Patton (Office Action mailed August 11, 2004, 5). The rejection was withdrawn in the Answer upon the filing of a terminal disclaimer (Answer 5).

Edwards is cited for teaching particles “incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, methods of preparation, and administration.” (*Id.*). Surfactants include dipalmitoylphosphatidylcholine (DPPC), and exemplary hydrophilic or hydrophobic complexes include insulin and protamine (*id.*). Moreover, according to the Examiner, the formulations of Edwards may include one or more excipients such as sugars, proteins, and surfactants (*id.* at 4). In addition, “Edwards discloses that administration of the particles to the lung by aerosolization permits deep lung delivery of relatively large diameter therapeutic aerosols, for example greater than 5 micron in mean diameter. The particles can be fabricated with features which enhance aerosolization via dry powder inhaler devices, and lead to lower deposition in the mouth, throat and inhaler device.” (*Id.*).

The Examiner cites Example 9 of Edwards, which discloses particles containing 60% DPPC, 2% insulin, 19% albumin, and 19% lactose (*id.*). The particles are made from solutions of the ingredients, which are combined and spray dried to produce the particles (*id.*).

The Examiner concludes:

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the formulations of Patton containing insulin, buffers and carriers with insulin formulations and methods of delivering the insulin formulations to the lung as taught by Edwards and to have implemented DPPC as the carrier, since it was disclosed that DPPC is an exemplary surfactant, naturally occurring in the lung.

Id. at 4-5.

In the Appeal Brief, Appellants do not contest the *prima facie* case of obviousness. Instead, Appellants argue that “the evidence of record, presented in the enclosed Rule 132 Declaration, establishes significant unexpected results. Thus, the selection of the presently claimed approximate amounts of 60% DPPC, 30% insulin and 10% citrate combination is patentable over the myriad of possible combinations derived from the combination of Patton and Edwards.” (Br. 3.)

According to Appellants,

The results pointed to the fact that DPPC concentration is not the sole predictor of the insulin formulation, but in fact a critical balance of insulin, DPPC and solution concentration achieved [by] the formulation. Figure 2, for example, shows that 10% insulin formulations “crash out” of solution rapidly, ranging from 5 minutes to two hours depending upon the concentration of insulin comprising the 10% formulation. On the other hand, the 30% insulin formulation does not crash out of solution *at all*. In other words, at concentrations as low as 10 g/L of the total solids (DPPC/insulin/citrate; 4 g/L DPPC), the 10% insulin containing formulation was unstable compared to the 30% insulin containing formulation where stability was observed even at 20 g/L of the total solids (12 g/L of DPPC).

(*Id.* at 5 (emphasis in original)).

Appellants assert that the above results could not have been predicted based solely on DPPC solubility, “and results in a dramatic improvement in manufacturability of the formulation that could have been predicted.” (Br. 5-6.) According to Appellants, “[t]he Examiner’s conclusion that these results are not significant is simply unsubstantiated.” (*Id.* at 6.) Appellants argue that the “132 declaration clearly shows the criticality of the presently claimed formulation (not a *range* of formulations . . . but . . . a *superior species* of formulation), having particles comprising, by weight,

approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate possesses unexpected properties as compared to formulations that are even *closer* than those of the combination of prior art cited by the Examiner.” (*Id.* (emphasis in original).) Appellants conclude that their “showing of unexpected enhanced stability and manufacturability of the presently claimed *specific* formulation is sufficient to overcome any *prima facie* case of obviousness in view of the potentially infinite combinations of formulations provided by the excipients and ranges disclosed in the cited combination of Patton and Edwards.” (*Id.* at 7.)

The 132 Declaration of Jennifer Schmitke states on page 1 that the claimed invention “results from substantial experimentation that necessitated the selection of a formulation that achieves serum insulin levels similar to that achieved by injectable insulin, good to excellent bioavailability, good to excellent physical stability and good to excellent manufacturability.”

Figure 2 of the Declaration is a graph of “crash-out” time, *i.e.*, the time before particles start to come out of solution, versus the percent insulin composition, with the different curves representing different concentrations (Declaration, 5). Figure 2 is reproduced below:

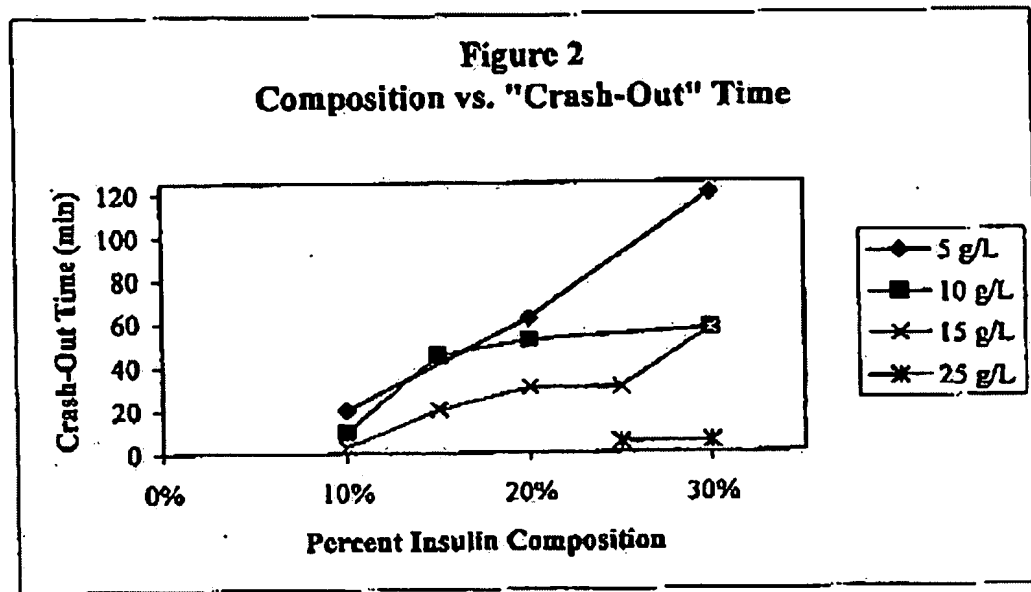


Figure 2 demonstrates that higher insulin content solutions appear to stay in solution longer (*id.*). According to the Declarant,

the 10% insulin formulation experienced rapid “crash-out” times with a DPPC concentration of 4.0 g/l, an insulin concentration of 0.5 g/l and a citrate concentration of 0.5 g/l. However, the 30% insulin formulation did not “crash-out” even at concentrations of 10 g/l total solids, resulting in a DPPC concentration of 12.0 g/l, an insulin concentration of 6 g/l and a citrate concentration of 2 g/l. Clearly, the solubility of the insulin formulation is not dictated solely by DPPC solubility. Such a dramatic improvement in manufacturability could not have been predicted.

(*Id.* at 5-6.)

At oral argument, Appellants stated that these results were not appreciated until after the filing of the present application, and are part of the routine experimentation known to the ordinary artisan in developing the manufacturing process. In addition, Appellants also stated that what Figure 2 is demonstrating is an interaction occurring between the components of the

composition, such as the insulin and the DPPC, and that such an interaction could not have been predicted.

The Specification teaches “[f]ormulations having particles comprising, by weight, approximately 40% to 60% DPPC, approximately 30% to about 50% insulin and approximately 10% sodium citrate.” (Specification 3). The Specification does not disclose the criticality of formulations of approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate.

PRINCIPLES OF LAW

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.” *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (citations omitted).

The burden of demonstrating unexpected results rests on the party asserting them, and “it is not enough to show that results are obtained which differ from those obtained in the prior art: that difference must be shown to be an *unexpected* difference.” *In re Klosak*, 455 F.2d 1077, 1080, 173 USPQ 14, 16 (CCPA 1972). “Mere improvement in properties does not always suffice to show unexpected results.” *In re Soni*, 54 F.3d 746, 751, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995). Moreover, it has been long held that “even though applicant’s modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art, unless the claimed ranges ‘produce a new and unexpected result which is different in kind and not

merely in degree from the results of the prior art.” *In re Huang*, 100 F.3d 135, 139, 40 USPQ2d 1685, 1688 (Fed. Cir. 1996) (quoting *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (1955), and citing *In re Woodruff*, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990)).

ANALYSIS

As to the prima facie case of obviousness, Appellants do not contest it in the Brief,³ thus, for the purposes of this Appeal, we conclude that Appellants concede that the Examiner has met the burden of establishing a prima facie case of obviousness.

We find that Appellants have not demonstrated that the formulation of claim 1 has unexpected properties so as to rebut the prima facie case of obviousness, and the rejection is affirmed.

Focusing on Figure 2, it is unclear what is unexpected. First, Appellants asserted at oral argument that the Figure demonstrates that the insulin and the DPPC of the Formulation of claim 1 interact with one another. However, Appellants have not presented any evidence that such interaction would be unexpected.

For example, Edwards teaches particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively charged or

³ Appellants state in the Reply Brief at page 2 that they have not admitted, either explicitly or inferentially, that the Examiner has established a prima facie case of obviousness. But as they do not point to any arguments made in the Appeal Brief attacking the prima facie case, and also do not present any argument as to why the Examiner failed to establish a prima facie case in the Reply Brief, we find Appellants have conceded the merits of the prima facie case for purposes of this Appeal. 37 C.F.R. § 41.37(c)(1)(vii).

negatively charged therapeutic agent and a molecule of opposite charge for delivery to the pulmonary system (Edwards, col. 3, ll. 55-60). Moreover, Edwards also teaches that “[i]f the agent to be delivered is negatively charged (such as insulin), protamine or other positively charged molecules can be added to provide a lipophilic complex which results in the sustained release of the negatively charged agent. Negatively charged molecules can be used to render insoluble positively charged agents.” (*Id.* at col. 7, ll. 5-10.) Thus, Edwards demonstrates that it was known in the art that interactions of molecules, such as charge-charge interactions, could change the solubilities of the molecules. Thus, the fact that the surfactant DPPC and negatively-charged insulin interact with one another to increase the crash-out time of higher concentration solutions containing higher levels of insulin is not necessarily unexpected.

Second, Figure 2 is the result of testing that is well known to the ordinary artisan that would be performed in developing and optimizing the manufacturing process. Thus, the modification of using higher insulin content would have been well within the skill level of the ordinary artisan. In addition, Appellants have not presented evidence that it is unexpected in such testing that formulations containing lower insulin concentrations would crash out sooner than formulations containing higher insulin concentrations.

Third, each concentration of the formulations presented on Figure 2 follows a curve, from which the position of additional points on each curve could be predicted. The only point that seems to fall outside of the curve is the 30% insulin solution having a concentration of 15 g/l. But it is unclear if that point is an actual outlier or merely a result of experimental error, as no error bars are presented.

Fourth, even if we accept the validity of the data, while the 10% insulin formulations crashed out of solution at lower concentrations than the 30% insulin formulations, we find that it is more a difference in degree, and not a difference in kind, which is required to support a finding of unexpected results.

CONCLUSIONS OF LAW

We conclude that the Examiner has set forth a prima facie case of obviousness that has not been contested by Appellants, and that the Declaration of Jennifer L. Schmitke, submitted under 37 C.F.R. § 1.132, does not demonstrate unexpected results sufficient to rebut the prima facie case.

CLAIMS 18, 20-39, AND 41-57

Appellants argue that claim 18 is separately allowable “because claim 18 recites that the formulation is administered to the patient in a single, breath-actuated step, a limitation not disclosed by Patton and Edwards.” (Br. 10.) Moreover, according to Appellants, “[c]laim 39 . . . recites simultaneous inhalation and dispersion of the particles from a receptacle containing the particles (e.g., breath actuated administration). Neither Patton nor Edwards disclose or make obvious this feature which is unique to the presently claimed particle formulation.” (*Id.*)

Thus, the issue as to both claim 18 and claim 39 is does the combination of references render obvious a method of delivering the composition of claim 1 by a breath-actuated step. According to the Examiner, the prior art establishes that a single, breath-actuated step would

have been obvious to the ordinary artisan as such methods were known and practiced in the art (Answer 4-5).

The Specification teaches at page 26 that “[v]arious suitable devices and methods of inhalation which can be used to administer particles to a patient’s respiratory tract are known in the art,” and lists a number of suitable prior art inhalers, as well as “others, such as known to those skilled in the art.” In addition, both Patton (for example, see the abstract) and Edwards (see, for example, column 25, Example 12) teach the delivery of particles of insulin to the lungs, but do not specifically teach the use of a breath-actuated inhaler.

The panel cites Bacon (U.S. Patent No. 5,503,144, issued April 2, 1996) to demonstrate that breath actuated dry powder inhalers and their use were known in the art, and thus, it would have been obvious to dispense the formulation of claim 51 using any dry powder inhaler known to the ordinary artisan, such as that taught by Bacon. The rapid release of insulin would be an inherent result of the delivery of the formulation of claim 5 to lungs using such breath-actuate, dry powder inhalers. Because our reasoning differs from that of the Examiner, and in order to give Appellants an opportunity to respond, we designate this affirmance as new grounds of rejection under 37 C.F.R. § 41.50(b).

CONCLUSION

In summary, we affirm the rejection of claims 1, 3-18, 20-39, and 41-60. Because our reasoning as to claims 18, 21-39, and 41-57 differs from that of the Examiner, we designate the rejection as to those claims only as new grounds of rejection.

Regarding the affirmed rejection(s), 37 C.F.R. § 41.52(a)(1) provides "[a]ppellant may file a single request for rehearing within two months from the date of the original decision of the Board."

In addition to affirming the Examiner's rejection(s) of one or more claims, this decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the appellants elect to prosecute further before the Examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the Examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

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If the appellants elect prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

AFFIRMED; 37 C.F.R. § 41.50(b)

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